STUDY OF THE ROLE OF MIRO, MITOCHONDRIAL OUTER MEMBRANE PROTEIN, IN *DROSOPHILA* MODEL OF ALZHEIMER'S DISEASE

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4. Summary

In summary, our observations suggest that overexpression of *Miro* modulates the AD-related pathologies in *Drosophila* by decreasing the rough eye phenotype, improving the behavioral defects such as phototaxis and climbing activity along with reducing apoptosis, increasing the ATP level and decreasing oxidative stress and neurodegeneration in the AD model flies. On the other hand, knockdown of *Miro* enhanced rough eye phenotype, climbing and phototaxis defect as well as increased ATP deficiency in AD model flies. Thus, it was suggested that Miro act as a key player in the modulation of AD-related pathologies.

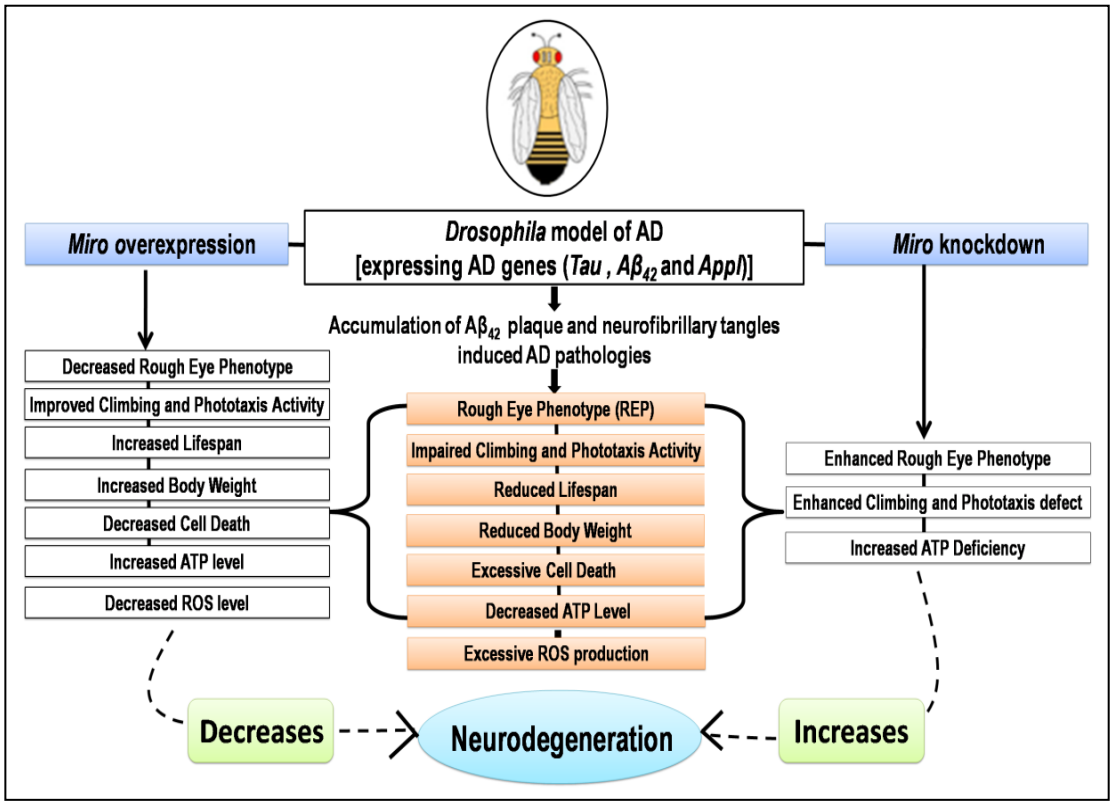

Figure: S1: Summary figure showing the effect of overexpression/knockdown of *Miro* in the modulation of AD-related pathologies in AD model flies

Chapter 1

Miro, a mitochondrial outer membrane protein genetically interacts with Alzheimer's disease genes (*Tau*, *Aβ$_{42}$* and *Appl*) in *Drosophila*

1.1 Introduction

As mentioned in the literature review, *Miro* is a mitochondrial Rho GTPase play a vital role in the mitochondrial axonal transport via forming a major protein complex with milton (an adaptor protein), kinesin and dynein (motor proteins). Apart from mitochondrial axonal transport, *Miro* also regulates mitochondrial dynamics (fission and fusion) and maintains mitochondrial structure and its physiological function. Previous studies have shown that improper axonal transport and altered mitochondrial dynamics are the key pathologies associated with AD. Since, Miro plays a crucial role in the regulation of mitochondrial axonal transport and its dynamics, it might be a key target for designing the novel therapeutic target for AD.

Chapter 2

Miro plays a regulatory role in the AD-related pathologies in Drosophila

2.1. Introduction

As shown in chapter 1, overexpression/knockdown of Miro modulates the AD-related pathologies such as rough eye phenotype, behavioral defects (phototaxis and climbing), reduced survival and body weight. Since, several molecular mechanisms such as abnormal mitochondrial dynamics (fusion and fission), reduced ATP level and excessive oxidative stress are one the key pathologies of AD which are responsible for induction of above mentioned AD-related pathologies (Ijima et al., 2009; Panchal and Tiwari, 2018; Panchal and Tiwari, 2020). Thus, in this chapter, we have checked the regulatory role of Miro on mitochondrial dynamics (fusion and fission), ATP level and mitochondrial and cytosolic oxidative stress in AD model flies.

Chapter 3

Overexpression of Miro reduces the cell death and decreases the neurodegeneration in AD model flies

3.1. Introduction

As shown in the chapters 1 and 2, overexpression/knockdown of Miro modulates the AD-related pathologies such as rough eye phenotype, defective phototaxis and climbing activity, reduced survival and body weight via increasing the mitochondrial fusion, ATP level and decreasing the oxidative stress in AD model flies. As it has been well reported that excessive cell death is also one of the key pathologies associated with AD and it induces neurodegeneration (Fricker et al., 2018; Gorman et al., 2008). Moreover, AD model flies also showed excessive cell death and neurodegeneration in neuronal tissue. Thus, in this chapter, I have examined the effect of Miro on the cell death (apoptosis) and neurodegeneration in AD model flies.

5. Conclusions

On the basis of above results the following conclusions were drawn

Chapter 1

- Overexpression/knockdown of *Miro* modulate rough eye phenotype and phototaxis activity associated with AD model flies
- Overexpression of *Miro* decreases the cell death in third instar larval eye imaginal discs of AD model flies
- Overexpression of *Miro* increases climbing activity, survival and body weight associated with AD model flies

Chapter 2

- Overexpression of *Miro* increases the mitochondrial average length in third instar larval eye discs of AD model flies via increasing the mitochondrial fusion gene, *Mitofusin* expression level
- Overexpression of *Miro* increases the ATP level in AD model flies
- Overexpression of *Miro* decreases the mitochondrial and cellular oxidative stress in AD model flies

Chapter 3

- Overexpression of *Miro* decreases the cell death (apoptosis) in third instar larval eye and brains of AD model flies
- Overexpression of *Miro* decreases the vacuolated regions in the adult brains of AD model flies and thus reduced the neurodegeneration in adult brains of AD model flies

Thus, it was concluded that *Miro* genetically interacts with AD-related genes (*Tau*, $A\beta_{42}$ and *Appl*) in *Drosophila*.